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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,478	04/16/2004	Mingjie Zhang	WILKG5.001AUS	1295

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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
PETERSEN, CLARK D	

ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 09/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/826,478	ZHANG ET AL.	
	Examiner	Art Unit	
	Clark D. Petersen	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 12-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on July 17, 2006 is acknowledged.

Claims 10 and 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Groups, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 17, 2006.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 16-19, 21, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Tochio et al (J Mol Biol, 2000). Tochio et al teach a method of testing the effect of a potential binding partner of PDZ2 of PSD-95. In particular, they test the effect of binding of a peptide that is a C-terminal fragment of the protein CAPON (see Results and Discussion, p. 227 col. 2, for example). The binding of CAPON to a ^{15}N-labeled PSD-95 PDZ2 was used to compare the bound vs. unbound conformation of PSD-95 PDZ2. From these data, a chemical shift figure was generated (see Fig. 5, p. 231, for example). In particular it was noted that CAPON binding induced strong shifts in αB and βB of PSD-95 PDZ2 (see p. 228 col 1, for example). In particular, the

residues GLGF, which are residue numbers 169-172, undergo a large chemical shift in response to binding by a ligand (see text, p. 227 col 1; see Fig. 5, p. 231, as examples). The sequence used in the experiments was that of rat PSD-95 PDZ2 (see Materials and Methods, p. 232, col 1, for example), which is the protein of SEQ ID NO:4 in the instant application. This sequence has greater than 50% homology to human PSD-95 PDZ2 as well. Furthermore, due to their strong sequence similarity, the analogous rat and human PSD-95 full length as well as isolated PDZ2 (i.e. SEQ ID Nos: 1, 3, 5 and 7) nucleic acid sequences would bind to each other in a stringent Northern blot.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 and 12-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tochio et al in view of Lee et al (Neuroscience Lett, 2000) and Aarts et al (Science, 2002).

The teachings of Tochio et al are discussed above and applied as before. Tochio et al do not expressly teach the application of flavonoids in a method of inducing conformational changes in PDZ2 of PSD-95 that are observable by NMR.

Lee et al teach the administration of flavonoids related to the catechin molecule, which are present in green tea. Lee et al teach that it is known in the art that green tea

has a protective effect against neuronal damage (see p. 191, col 2, for example) and ameliorates brain damage during ischemia (see p.192, col 2, for example), and that part of this neuroprotective effect is attributable to flavonoids. They test the effect of administration of a flavonoid, EGCG, on gerbils after during artificially-induced brain ischemia. They report that administration significantly increases the number of neurons surviving the brain injury (see Fig. 2, p. 194, for example). They speculate that part of the neuroprotective effect they observe may be due to inhibition of neuronal nitric oxide synthase (nNOS) activity, which plays an important role in pathophysiological processes including neurotoxicity (see p. 194, for example).

Aarts et al teach that it is well known in the art that PSD-95 binds to nNOS and NMDA receptors through its second PDZ domain (see p. 846, for example). They also teach that it is known in the art that blocking the interaction between NMDA receptors and PSD-95 (by removing PSD-95 entirely, for example) dissociates NMDA receptor from nitric oxide production and suppresses excitotoxicity, which is a cause of neuronal death and brain damage during brain injury. Aarts et al constructed a peptide that interacts with the PDZ2 domain of PSD-95, thus blocking its interaction with NMDA receptor, and introduced it into rat neurons; this peptide interacted with the endogenous, full-length PSD-95. Because of the strong similarity between rodent and human PSD-95 sequences, it is obvious that their experimental findings are attributable not just to rat neurons, but provide guidance as to the mechanism of human PSD-95, as well. They teach that this peptide inhibits nitric oxide production (determined by measuring its

correlate, cyclic GMP), and enhances survival of neurons exposed to excitotoxic NMDA (see text p.847; see Fig. 2 panel E p. 848; see Fig. 3 panel A, p. 849, as examples).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to study the action of flavonoids on the conformation of PDZ2 of PSD-95 in a method of testing agents for their protective effect against brain damage, because Tochio et al teach that it is possible to use NMR to study conformational changes in PDZ2 of PSD-95 in response to a ligand, Aarts et al teach that ligand binding of PDZ2 of PSD-95 enhances neuronal survival by blocking nitric oxide production, and Lee et al teach that flavonoids from green tea protect against brain damage, and suggest the effect of flavonoids may be due to inhibition of nitric oxide production. One would have been motivated to do so for the expected benefit of better determining why flavonoids have a neuroprotective effect during brain injury events such as stroke.

Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, one would have had a reasonable expectation of success in practicing the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Clark D. Petersen whose telephone number is (571)272-5358. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571)272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RALPH GITOMER
PRIMARY EXAMINER
GROUP 1200

CDP
9/14/2006